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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/565,885	01/25/2006	Juan Lopez De Silanes	2099.0080000	8053

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STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
SKELDING, ZACHARY S	
ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
12/01/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/565,885	LOPEZ DE SILANES ET AL.	
	Examiner	Art Unit	
	ZACHARY SKELDING	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *62-72,76 and 77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *62-72,76 and 77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's remarks filed October 1, 2010 are acknowledged.

   Claims 62-72, 76 and 77 are pending.

   The previous grounds of rejection can be found in the Office Action mailed April 1, 2010.

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

   (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 62, 64 and 65 stand rejected under 35 U.S.C. 103(a) as being unpatentable over John Pluenneke (US 2001/0021380) in view of Fabrizio et al. (EP 0 492 448 A1), Horwitz (WO 92/22324, cited on an IDS), Adair et al. (EP 0 516 785 B1) and Reza Dana (WO 00/27421), essentially for the reasons of record as put forth in the prior Office Action mailed April 1, 2010 as further described below.

   Applicant argues the claimed methods of treatment are non-obvious because "one of ordinary skill would have considered the ability of antibody fragments to penetrate the cornea differently than the ability to penetrate other tissues, such as tumor tissue, because of the physiological differences between the cornea and other tissues," and because based on the effectiveness of topical anti-TNFα F(ab')2 in animal model experiments performed in Dr. Paniagua-Solis' laboratory he asserts "it is my opinion that the increased graft cornea survival and decreased morphological properties of the cornea associated with graft rejection would not have been expected in view of the art cited by the Examiner."

   Applicant's arguments have been considered, but have not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed April 1, 2010.

   As to applicant's arguments concerning the different physiology of the cornea vs. tumor tissue, and how "one of ordinary skill would have considered the ability of antibody fragments to penetrate the cornea differently than the ability to penetrate other tissues, such as tumor tissue, because of the physiological differences between the cornea and other tissues," the examiner acknowledges that these tissues are physiologically distinct.

   That said, the examiner disagrees with applicant's conclusion that "one of ordinary skill in the art would not have necessarily expected that the improved penetration of F(ab')2 fragments into tumor tissue disclosed in Horwitz would apply to the penetration of F(ab')2 fragments into non-tumor tissues such as cornea tissue."

Regardless of the physiological differences between these tissue it remains the examiner's position that for any given tissue / biomolecule, one of ordinary skill in the art would be inclined to believe that by decreasing the size of the biomolecule it would generally increase diffusion of the biomolecule through the tissue. Thus, even if a tumor is different from post-operative corneal tissue, one of ordinary skill in the art would still be inclined to believe that a smaller molecule, e.g., an F(ab')2 antibody fragment, would tend to better penetrate the post-operative corneal tissue than a larger molecule, e.g., intact antibody or a soluble TNF receptor-Fc fusion protein.

This notion is consistent with the teachings of Jain, R.K., Cancer Metastasis Rev., 9:253-266, 1990, cited as Exhibit D with applicant's most recent response at page 262, right col. - page 263, left col, emphasis added:

"The third approach ***may be based on increasing the interstitial transport rate of molecules***. Use of cocktails of antibodies may not overcome this problem because each antibody has to cross the same physiological barriers. ***One method of accomplishing this goal would be to use lower molecular weight agents, e.g., antibody fragments F(ab')2 and Fab. While the fragments have higher values of P [vascular permeability] and D [interstitial diffusion coefficient] compared to the intact antibody and hence, penetrate deeper into tumors***, there are two physiological problems associated with their use - they are eliminated more rapidly from blood, and their uptake into normal tissues is also increased. The elimination problem can be overcome by repeated or continuous injections of nonimmunogenic fragments of chimeric or human antibodies. However, as the molecular weight is lowered further, the normal tissue toxicity problem may become more pronounced similar to that encountered with conventional anticancer agents (molecular weight <2,000) [52, 53]. Some of the problems with the systemic toxicity may be overcome by local injection (e.g., intra-arterial, interstitial, intraperitoneal) at the cost of not being able to reach the distant metastases. If the toxicity to normal tissue could be overcome, combination of local and systemic injections would be more effective. Similarly, delivering low molecular weight agents (e.g., drug, toxin, enzyme, hormone) linked to MAbs and releasing them once they have extravasated or entered cells seems reasonable. However, once a small molecule is uncoupled from the antibody it may diffuse back into a nearby blood vessel, and may be rapidly eliminated.

Ideally, an antibody should have a high specificity and low molecular weight. To this end, recent developments in producing recombinant DNA monoclonal antibodies have already yielded smaller antibody fragments (e.g., antibody binding site, molecular recognition unit). In addition, two other approaches seem to satisfy the requirement of low molecular weight with increased specificity…"

Furthermore, applicant continues to fail to address a number of additional reasons why one of ordinary skill in the art would have had a reasonable expectation of successfully practicing the claimed method of treatment and would have been motivated to do so.

For example, as put forth in several prior Office Actions, see, e.g., the Office Action mailed April 1,2010 at page 4, 5th paragraph and the Office Action mailed July 31, 2009 at page 3, 6th paragraph, why would one of ordinary skill in the art consider corneal penetration unpredictable, especially so when a larger TNFα antagonist that binds FcR, such as the TNFR-Fc antagonist exemplified by Reza Dana (@150 kDa vs. @100 kDa), is capable of treating corneal transplant rejection in a mouse model?"

Also, as put forth in the prior Office Action at page 3-4 bridging paragraph the physiological differences between a tumor and the post-operative cornea would make penetration of the tissue by an F(ab')2 fragment more, not less, predictable (emphasis added):

"…the claimed invention involves the treatment of corneal transplant rejection patient, and as would be well known to one of ordinary skill in the art the surgical procedure for corneal transplantation involves trephining of both the donor and recipient cornea and suturing of the donor cornea onto the trephined recipient cornea (see, e.g., the Merck Manual of Diagnosis and Therapy, Mark Beers and Robert Berkow, eds., Published by Merck Research Laboratories, 17th ed., 1999, page 723, left column, last paragraph). ***Thus, unlike the case of a healthy cornea a hole has been cut in the recipient cornea and this hole has been covered with the donor cornea, the two layers being attached by sutures. Accordingly, it would not be surprising to one of ordinary skill in the art if a therapeutic molecule could pass through a transplant recipients cornea more readily than an intact cornea***."

Furthermore, unlike in the case of a tumor where the drug or biologic agent generally has to make its way from the blood stream to the tumor, a drug or biomolecule, such as an F(ab')2, can be administered to the post-operative cornea in the presence of other constituents suitable for increasing corneal penetration as put forth the prior Office Action at page 4, 1st paragraph:

"Furthermore, it worth noting that the instant claims encompass in their breadth the use of opthalmically acceptable carriers, including dermatologically acceptable gel vehicles, and such a practice has been demonstrated by the cited prior art to increase the delivery of drugs to the cornea. For example, Reza Dana teaches the administration of TNFR-Fc in a vehicle containing sodium hyaluronate which increases viscosity and drug delivery to the surface epithelium (see Dana, e.g., at page 5-6 bridging paragraph; page 9, 1st paragraph; the paragraph bridging pages 17-18 and claim 8)."

Also, applicant's argument focuses on the tissue penetrating abilities of F(ab')2 fragments to the exclusion of other reasons that one of ordinary skill in the art would have been motivated to use F(ab')2 fragments for the treatment of corneal transplant rejection.

For example, as put forth in the Office Action mailed September 15, 2008 at page 5, 3rd paragraph, "Given the reference teachings, it would have been obvious to one of ordinary skill in the art, and one of ordinary skill in the art would have been motivated to treat corneal allograft rejection with an $F(ab')_2$ fragment of an anti-TNFα antibody since such fragments

have a number of generally useful features such as their ease of production and low immunogenicity (relative to intact non-human antibodies), and TNFα antagonistic activities equivalent to intact antibodies…"

As to the opinion of Dr. Paniagua-Solis put forth in the Declaration under 37 CFR § 1.132 filed November 2, 2009, first applicant describes Dr. Paniagua-Solis qualifications as put forth in his curriculum vitae filed November 2, 2009 in conjunction the Declaration under 37 CFR § 1.132 and then asserts,

"In view of his curriculum vitae, it is clear that Dr. Paniagua- Solis was an active and experienced researcher in immunology at the time the present application was filed and therefore would be considered a person of at least ordinary skill in the art…The Examiner has not provided any reason why Dr. Paniagua-Solis would not be considered a person of ordinary skill in the art."

(see remarks page 10, 1st paragraph).

First and foremost, the examiner would like to point out that he did not and would not say that Dr. Paniagua-Solis is not "at least a person of ordinary skill in the art." Dr. Paniagua-Solis certainly is "at least a person of ordinary skill in the art," indeed he is an inventor of the claimed invention.

Applicant then goes on to recapitulate the Declaration filed November 2, 2009 in their own words (see remarks page 11) and concludes, "Applicants disagree that Dr. Paniagua-Solis has not provided a reason why he found the experimental results unexpected or why the art would have found the results unexpected. Rather, these statements by Dr. Paniagua-Solis provide a basis for his opinion that the evidence is unexpected, and therefore Dr. Paniagua-Solis' opinion is appropriate evidence under 37 C.F.R. § 1.132 that should be given due consideration."

In response the examiner would like to point out that he did not and would not say that the Declaration of Dr. Paniagua-Solis was not "appropriate evidence under 37 C.F.R. § 1.132 that should be given due consideration."

Rather, as put forth in the prior Office Action at page 5, 2nd paragraph, the opinion of Dr. Paniagua-Solis "…is not found convincing because other than stating that in his opinion the results of the experiments presented in his declaration were unexpected, Dr. Paniagua-Solis makes no case why he found these results to be unexpected or why the art as whole at his time of invention would have found these results to be unexpected. While Dr. Paniagua-Solis opinion is acknowledged, when Applicant's arguments and the Declaration of Dr. Paniagua-Solis are taken as a whole and weighed against the evidence supporting the *prima facie* case of unpatentability, the instant claims, by a preponderance of evidence, remain unpatentable. See M.P.E.P. § 716.01(d)."

Applicant then goes on to argue that a nexus exists between the opinion of Dr. Paniagua-Solis ("It is my opinion that the increased graft cornea survival and decreased morphological properties of the cornea associated with graft rejection would not have been expected in view of the art cited by the Examiner.") and the merits of the claimed invention, and then reminds the examiner that the obviousness of the claimed invention rests on a weighing of the prior art and evidence of record to determine if the claimed invention is or is not more likely than not obvious. (see remarks pages 12-14).

In response, the examiner agrees that a nexus exists between the opinion of Dr. Paniagua-Solis and the claimed invention, however that said when Applicant's arguments and the Declaration of Dr. Paniagua-Solis are taken as a whole and weighed against the evidence supporting the *prima facie* case of unpatentability, the instant claims, by a preponderance of evidence, remain unpatentable. See M.P.E.P. § 716.01(d).

In conclusion, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Thus, the instant claims stand rejected as unpatentable over Pluenneke, Fabrizio, Horwitz, Adair and Reza Dana.

4. Claim 63 stands rejected under 35 U.S.C. 103(a) as being unpatentable over John Pluenneke (US 2001/0021380) in view of Fabrizio et al. (EP 0 492 448 A1), Horwitz (WO 92/22324), Adair et al. (EP 0 516 785 B1), Looareesuwan et al. (Am J Trop Med Hyg. 1999 Jul;61(1):26-33, cited herewith) and Reza Dana (WO 00/27421), essentially for the reasons of record as put forth in the Office Action mailed April 1, 2010 and as further described in Section 3 above.

   Applicant argues claim 63 is not obvious for the same reasons that claim 62 is not obvious as put forth in Section 3 above.

   Applicant's argument has been considered but has not been found convincing essentially for the reasons of record as put forth in the Office Action mailed April 1, 2010 and as further described in Section 3 above.

5. Claims 66-72, 76 and 77 stand rejected under 35 U.S.C. 103(a) as being unpatentable over John Pluenneke (US 2001/0021380) in view of Fabrizio et al. (EP 0 492 448 A1), Horwitz (WO 92/22324, cited on an IDS), Adair et al. (EP 0 516 785 B1) and Reza Dana (WO 00/27421) as applied to claims 62, 64 and 65 above, and further in view of the Merck Manual of Diagnosis and Therapy (Mark Beers and Robert Berkow, eds., Published by Merck Research Laboratories, 17th ed., 1999, pages 722-24) and Gerald DeVries (US

2003/0180294), essentially for the reasons of record as put forth in the Office Action mailed April 1, 2010 as further described below.

Applicant argues claims 66-72, 76 and 77 are not obvious for the same reasons that claim 62 is not obvious as put forth in Section 3 above.

Applicant's argument has been considered but has not been found convincing essentially for the reasons of record as put forth in the Office Action mailed April 1, 2010 and as further described in Section 3 above.

Applicant further argues claims 66-68 are not obvious because, "the cited references at best provide an extremely large number of potential options upon which one of ordinary skill in the art could combine to arrive at the claimed methods having the specified administration times following corneal transplant. While the Examiner may hone in on a particular composition and administration time following corneal transplant using the claimed methods as a starting point, this is applying hindsight reasoning in selecting which particular composition and which administration time, of the numerous possible options to use as a starting point." (see remarks pages 15-16 bridging paragraph).

Applicant's argument has been considered but has not been found convincing essentially for the reasons of record as put forth in the Office Action mailed April 1, 2010.

The element of claims 66-68 that applicant is arguing is non-obvious is the dosing limitation, e.g., "administered within 24 hours following a corneal transplant in a patient"; "administered within 2 hours following a corneal transplant in said patient"; "administered within 30 minutes following a corneal transplant in said patient" (claims 66-68, respectively).

As put forth in the prior Office Action at page 6, the cited art teaches some, but not all of the claimed dosing regimens.

For example, "Dana…teaches treatment of a mouse corneal transplant model system with TNFR-Fc topically administered 24 hours after transplantation and three times/day for the following 8 weeks (see page 17-18 bridging paragraph)." (see prior Office Action at page 6, 2nd paragraph).

As another example from page 6, 4th paragraph of the prior Office Action, "the administration of the anti-TNFα F(ab')2 both immediately following corneal transplantation as well as the weeks that follow is consistent with art recognized treatment using other immunosuppressants such as corticosteroids as described in the Merck Manual at page 723, right col."

Moreover, it is evident from the reference teachings that dosage and frequency of anti-TNFα F(ab')2 administration would be considered by one of ordinary skill in the art to be results effective variables subject to routine optimization. In this regard it is noted that "[w]here the

general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955), and see M.P.E.P. § 2144.05 II.A. Moreover, it is well settled that "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." In re Boesch, 617 F.2d 272,276, 205 USPQ 215, 219 (CCPA 1980). See also Merck & Co. v. Biocraft Labs. Inc., 874 F.2d 804,809, 10 USPQ2d 1843, 1847-48 (Fed. Cir. 1989) (determination of suitable dosage amounts in diuretic compositions considered a matter of routine experimentation and therefore obvious).

Thus, one of ordinary skill in the art would gather from the teachings of the prior art that immunosuppressive agents should be administered anywhere from immediately after transplantation, to 24 hours after and beyond to treat corneal graft rejection, subject to routine optimization. These teachings hardly represent "an infinite number of options."

As to claims 69 and 70 in particular, applicant further argues these claims are non-obvious in view of the declarative evidence of Dr. Paniagua-Solis.

Applicant's argument is acknowledged but is not found convincing for the reasons of record put forth in Section 3 above.

As to claims 71, 72, 76 and 77 in particular, applicant further argues these claims are non-obvious in view of the declarative evidence of Dr. Paniagua-Solis.

Applicant's argument is acknowledged but is not found convincing for the reasons of record put forth in Section 3 above.

In conclusion, when Applicant's arguments and the Declaration of Dr. Paniagua-Solis are taken as a whole and weighed against the evidence supporting the *prima facie* case of unpatentability, the instant claims, by a preponderance of evidence, remain unpatentable. See M.P.E.P. § 716.01(d).

In conclusion, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

6. No claims are allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until

after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZACHARY SKELDING whose telephone number is (571)272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Zachary Skelding/
Primary Examiner, Art Unit 1644